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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,250	06/22/2006	Glen R. Nemerow	5410-007 NATL	5019

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EXAMINER

SAJJADI, FEREDOUN GHOTB

ART UNIT	PAPER NUMBER
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1633

MAIL DATE	DELIVERY MODE
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11/28/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,250	NEMEROW ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 10-54 and 57-79 is/are pending in the application.
- 4a) Of the above claim(s) 1-7, 10-54, 57, 59-68 and 72-79 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 58 and 69-71 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 December 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/25/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response of September 11, 2007, to the Restriction Requirement dated July 13, 2007 has been entered. No claims have been amended, cancelled or newly added. Claims 1-7, 10-54 and 57-79 are pending in the application.

Election/Restrictions

Applicant's election of Group VIII (claims 58 and 69-71) with traverse, drawn to an adenovirus particle comprising a modified shaft fiber protein and a modification in the fiber knob to further reduce CAR binding; (SEQ ID NO: 48 corresponding to a modified last repeat), is acknowledged. Applicants' species election of AB loop or CD loop, is further acknowledged.

The traversal is on the grounds that it would not impose an undue burden to search and examine Groups V and VIII together. Applicants' arguments have been fully considered, but are not found to be persuasive, because Applicants have relied on U.S. restriction practice in a case where restriction has been properly applied under rules for Unity of Invention. PCT Rule 13.2, as it was modified effective July 1, 1992, no longer specifies the combinations of categories of invention which are considered to have unity of invention. The categories of invention in former PCT Rule 13.2 have been replaced with a statement describing the method for determining whether the requirement of unity of invention is satisfied. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. Thus, burden is not germane to restriction under rules of Unity of Invention. In the instant case, the inventions of Groups V and VIII are distinct, each from the other, as Group V claims include therapeutic compositions, and the special technical feature shared by the Groups (i.e. a modified adenovirus fiber protein shaft that in an adenoviral particle reduces binding to the CAR receptor), is anticipated by the prior art of Vigne et al. as set forth on p. 4 of the previous office action dated 7/13/2007. The restriction under PCT rules 13.1 and 13.2 is proper, and Applicants have not provided any evidence or arguments that Vigne et al. has been improperly applied. Furthermore, according to MPEP 1893.03(d), any nonelected processes of making and/or using an allowable product should be considered for rejoinder following the practice set forth in MPEP § 821.04(b).

The restriction requirement is deemed proper, maintained and made FINAL. Claims 1-7, 10-54, 57, 59-68 and 72-79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected subject matter, there being no allowable generic or linking claim.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Applicant timely responded to the restriction (election) requirement in the Papers filed September 11, 2007. Claims 58 and 69-71 are under current examination.

Information Disclosure Statement

The information disclosure statement filed 4/25/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been fully considered, since no foreign patent documents were present in the instant applications. Applicant is required to provide copies of the missing references to be considered by the examiner.

Objections to the Specification/Abstract

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825

37 CFR 1.821 (a) states: Nucleotide and/or amino acid sequences as used in §§1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an

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unbranched sequence of ten or more nucleotides. 37 CFR 1.821 (d) states: Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Neither the consensus sequence depicted in Figure 1B, nor the descriptions of the drawings refer to the consensus sequence by SEQ ID NO. As it is not clear whether the sequence of Figure 1B is present in the CRF listing, Applicants are required to check both the as filed paper and CRF sequence listings to ensure concordance with the sequences depicted in Figure 1B. The instant application may be placed in compliance with 37 CFR 1.821-1.825 by amending either the Figure or the brief description of the Figure to refer to appropriate SEQ ID NO.

Claim Objections

Claim 58 is objected to because of the following informalities: the claim has not been amended to recite the elected invention. The claim encompasses non-elected subject matter that include various modifications in the third β -repeat of the fiber shaft. Appropriate correction is required.

Claim 58 is objected for reciting, "modified fiber", instead of "modified fiber shaft", as the adenovirus fiber includes both the shaft and knob proteins, and the modifications recited in claim 1 are limited to those in the fiber shaft.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of

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this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 58 and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by Vigne et al. (U.S. Patent No.: 6,911,199; effective filing date: Aug. 27, 1998).

The instant claims encompass an adenovirus particle comprising a fiber shaft protein modified in a last full repeat and a modification in the fiber knob to further reduce CAR binding. The instant specification states that modifications include any mutation, such as a deletion, insertion or replacement of at least one amino acid in the fiber shaft (lines 23-25, p. 4).

Vigne et al. teach targeted adenovirus vectors for delivery of heterologous genes, wherein modifications of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Title and Abstract). Specifically disclosing that the fiber protein can be modified to have a fiber shaft that is shorter than a wild-type fiber shaft, in particular by an in-frame deletion or by replacing it with the shaft from another serotype (column 6). In Example 3, Vigne et al. teach a shortened Ad5 shaft that retained only 6 or 9 repeats instead of 22 in the native protein (column 30), and additionally teach using SOE35Kg primer corresponding to the last repeat of the Ad3 fiber shaft and primers that include modifications resulting in the creation of restriction sites to generate an intertypic fiber composed of the Ad5 tail, the Ad3 shaft and part of the Ad5 knob, and flanked with unique restriction sites (columns 31 and 32, bridging). The disclosed mutation thus encompasses a substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft. One mutant adenovirus thus generated (vBS1) was noted to bind less efficiently to CAR (column 33).

Vigne et al additionally teach that at least a part of the fiber HI loop (knob) is replaced with a ligand peptide or targeting sequence, so as to functionally display its binding specificity at the capsid surface, that may comprise deletion of about 6 to 17 amino acids from the hexon HI loop, preferably not exceeding 11 amino acids (column 4). Further teaching: "Capsid modifications that impair the native entry pathway (e.g. fibers displaying short shafts) can

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therefore be combined with capsid modifications that provide an additional, CAR-independent, pathway of infection.” (columns 47 and 48; bridging).

Therefore by teaching all the limitations of claims 58 and 69, Vigne et al. anticipate the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 58 and 69-70 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vigne et al. (U.S. Patent No.: 6,455,314; effective filing date: Aug. 27, 1998), in view of Wickham et al. (U.S. Patent No: 2002/0132343; effective filing date Sep. 11, 1998).

The instant claims encompass an adenovirus particle comprising a fiber shaft protein modified in a last full repeat and a further modification in the AB loop or CD loop of the fiber knob.

Vigne et al. describe targeted adenovirus vectors for delivery of heterologous genes, wherein modifications of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Title and Abstract). Additionally disclosing substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft (column 33). Vigne et al. further describe replacement of a part of the fiber HI loop (knob) with a ligand peptide or targeting sequence, that impair the native entry pathway and provide an additional, CAR-independent, pathway of infection.” (columns 47 and 48; bridging).

Vigne et al do not specifically describe fiber knob modification confined to the AB or CD loop. Wickham et al. describe adenoviral vectors that contain modifications in the Ad5 fiber knob. Multiple mutations are described as located in the AB loop, CD loop or HI loop (Table 1) that result in reducing CAR native receptor affinity of the resulting mutant particle (column 19; Table 2), thus providing for the deficiency of AB or CD loop in the teachings of Vigne et al., and providing the motivation to introduce mutations in the AB or CD loop.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine the teachings of Vigne et al. and Wickham et al. to include fiber knob mutations in either the HI, AB or CD loops, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention.. A person of ordinary skill in the art would have been motivated to introduce modifications in either the AB or CD lop of the fiber knob as taught by Wickham et al., because such mutations would provide an additional CAR-independent pathway of infection for adenovirus retargeting.

Claims 58 and 69-71 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vigne et al. (U.S. Patent No.: 6,455,314; effective filing date: Aug. 27, 1998), in view of Hallenbeck et al. (U.S. Patent No: 2002/0137213; effective filing date June 2, 2000),

The instant claims encompass an adenovirus particle comprising a fiber shaft protein modified in a last full repeat and a further modification in the fiber knob that include KO1.

Vigne et al. describe targeted adenovirus vectors for delivery of heterologous genes, wherein modifications of the internal sites of the adenovirus fiber protein that include short targeting peptides fused to the C-terminus of the fiber protein, or the fiber HI loop (knob) target the modified adenoparticles to specific cell types (Title and Abstract). Additionally disclosing substitution or replacement of the Ad5 shaft with Ad3, comprising a modification in the last full repeat of the fiber shaft (column 33). Vigne et al. further describe replacement of a part of the fiber HI loop (knob) with a ligand peptide or targeting sequence, that impair the native entry pathway and provide an additional, CAR-independent, pathway of infection.” (columns 47 and 48; bridging).

Vigne et al do not specifically describe the KO1 fiber knob mutation. Hallenbeck et al. describe adenovirus particles mutated in their fiber proteins that no longer bind to their natural cellular receptor and can be retargeted to a specific cell type through the addition of a ligand to the virus capsid (Abstract). Hallenbeck et al. specifically described are adenoviral constructs containing the KO1 fiber AB loop mutation (Fig. 9), displaying a diminished interaction with CAR (paragraph [0092])), thus providing for the deficiency of KO1 modification in the teachings of Vigne et al., and additionally providing the motivation to introduce the KO1 modification in the fiber knob region. Adenoviral vectors containing the KO1 mutation in conjunction with a ligand targeting moiety are described in Example 3.

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine the teachings of Vigne et al. and Hallenbeck et al. to introduce the KO1 mutation as the fiber knob mutation in a retargeted adenoviral vector, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to introduce the KO1 modification in the fiber knob as taught by Hallenbeck et al., because such mutations would provide an additional CAR-independent pathway of infection for adenovirus retargeting.

Conclusion

Claims 58 and 69-71 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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